Compliance with tricyclic antidepressants: the value of four different methods of assessment

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Aims To assess the advantages and disadvantages of four methods for studying compliance with antidepressants: self-report scores, tablet counts, a microprocessor (MEMS) container system and the assay of nordothiepin and dothiepin concentrations in plasma.

Methods The techniques were used in 88 patients commencing tricyclic antidepressants in the setting of UK general practice.

Results The MEMS system proved to be the most informative technique allowing identification of the precise time of container opening, the demonstration of 'drug holidays' and early cessation of therapy. Self-report scores (Morisky) proved a useful screening technique with a sensitivity of 72.2% and specificity of 74.1% for $\geq 80\%$ compliance. Although tablet counts were possible in 84 patients (95.5%) they were unreliable in 19 (21.6%). Blood concentration assays proved the least acceptable method to patients and were possible in only 53 (60.2%). A ratio of nordothiepin:dothiepin ≥ 1.1 claimed, by others, to identify noncompliance was only reliable when concentrations were low.

Conclusions Both the MEMS system and self-report scores proved useful methods for identifying noncompliant patients in the setting of UK general practice. Although compliance was higher than reported in previous studies with 70 patients (79.5%) completing 6 weeks treatment, general practitioners tended to prescribe sub-therapeutic doses.

Keywords: antidepressants, compliance

Introduction

Depression is the fourth most important cause of disability in the world. In Britain, most depressed patients are managed in primary care and antidepressant drugs represent the mainstay of treatment. To-date, tricyclic antidepressants have been the most widely used group of drugs and still account for approximately 50% of all new prescriptions. The two most commonly prescribed tricyclic antidepressants are dothiepin and amitriptyline [1] and practice guidelines suggest that treatment with them should continue for at least 4–6 months [2].

The effectiveness of tricyclic antidepressants depends on both dosage and duration of therapy [2]. It is likely that poor compliance (adherence) is a major factor influencing treatment outcome [3], but its extent and the factors influencing it are not well understood. To date, most studies of compliance with antidepressant treatment have been carried out on hospital out-patient populations. Furthermore, almost all previous studies have relied on indirect methods of assessment including self-reporting of tablet consumption and the counting of left-over tablets. More recently, mechanical devices such as the microprocessor-based Medication Event Monitoring System (MEMS) have been developed. These record the precise time of opening of the tablet container. The assay of blood for drug and its metabolites has also been used [4, 5]. Ilett and colleagues [6] have suggested that for dothiepin a ratio of nordothiepin:dothiepin of greater than 1.1 indicates noncompliance for a period of 48 h or longer.

The overall aim of the present study was to evaluate the relative merits of four different methods of compliance

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assessment, namely patient reports, tablet counts, the use of the MEMS microprocessor system and the ratio of nordothiepin:dothiepin and nortriptyline:amitriptyline concentrations in blood.

Methods

Recruitment of subjects

Local general practices were asked to refer any patients aged 18 years or over who were commencing on treatment with either dothiepin or amitriptyline. The study was approved by all the relevant local ethics committees. Patients were excluded if they had received either of these medicines within the past 3 months or had a significant contra-indication including allergy, heart disease, glaucoma, pregnancy or were receiving incompatible medicines. Patients deemed to be at a significant risk of suicide were also excluded. This paper deals with a group of patients who were recruited consecutively and whose medication was dispensed in Medication Event Monitoring System (MEMS) containers. All of these patients participated in a larger randomised controlled trial [7] assessing the effects of two interventions designed to improve compliance.

Study design

As part of the larger randomised controlled trial, subjects were followed up for 12 weeks from the start of dothiepin/amitriptyline treatment. Prior to their involvement, patients received both verbal and written information about the study which looked 'at the effects of one form of treatment for depression and related problems'. All interviews and interventions were carried out in the subjects' homes. Within 48 h of referral, they were visited by a research nurse for about 1 h, and again at 6 weeks and 12 weeks. The patients were randomised into four groups:

Group 1 (23 patients) did not receive any intervention

Group 2 (20 patients) received a prescription information leaflet in a sealed envelope at the end of the first interview.

Group 3 (23 patients) had behavioural and educational intervention visits by a nurse at 2 weeks and 8 weeks.

Group 4 (22 patients) had both leaflet and intervention visits.

The interviewing nurse was blind to any intervention.

Supply of medication

Following receipt of faxed instructions from the general practitioners (which included the dose of dothiepin or amitriptyline) medication was dispensed in MEMS containers, sufficient for a period of 3 weeks. This was delivered by the nurse to the patient at the end of the first interview conducted in the patient's home. At the end of 3 weeks the container was replaced with a further supply to last until 6 weeks after recruitment. Further visits were made to supply medication as needed if the GP changed the dose. If at the 3 week visit, the patients admitted having stopped taking their medication, the container was collected early and the final interview was brought forward.

Compliance measures

1 *Patient reports*

At the 6 week interview all subjects were asked the following four standard questions described by Morisky and colleagues [8]

Do you ever forget to take your medication?

Are you careless at times about taking your medicine?

When you feel better, do you sometimes stop taking your medicine?

Sometimes when you feel worse, do you stop taking your medicine?

Each 'Yes' scored 1: consequently, a score of 0 would suggest no problem with medicine taking and hence good compliance, whereas the maximum of 4 could indicate major difficulties and suggest poor compliance.

2 *Pill counts*

The number of tablets/capsules issued and the number remaining in the bottle were recorded and the difference compared with the number that should have been taken according to GP's instructions. The number actually removed was expressed as a percentage of the number which should have been taken.

3 *MEMS*

Medication was supplied as described above. A microchip in the MEMS lid recorded the exact time of each opening of the container [9]. The lids were shipped to AARDEX Ltd (Switzerland) for downloading via their computer. Their printouts listed the opening times and the percentage of days the correct number of doses were 'taken'. However, from the viewpoint of therapeutic outcome the latter was judged to be more important and was chosen for subsequent comparisons. Figures between 80 and 100% were taken as indicating satisfactory levels of compliance.

4 *Blood tests*

Blood was taken from all subjects who consented to this procedure. The first sample was timed as close as possible to 12 h after the first reported dose, the second at 6 weeks or when medication was stopped, if earlier. Venous blood (12 ml) was taken with a needle and syringe and transferred to lithium heparin tubes. Plasma was separated

by centrifugation, frozen, and later analysed for dothiepin or amitriptyline and their metabolite concentrations by h.p.l.c. [10] using amitriptyline and dothiepin as internal standards, respectively. The ratio of metabolite to parent drug was calculated [6].

Statistics

Sensitivity and specificity analyses were undertaken for the Morisky scores [8] by comparison with the data from the MEMS recordings. Comparisons were undertaken between Morisky scores and the number of patients who opened their container on every day; on 90% or greater of days and on $\geq 80\%$ of study days. Least squares regression analyses were undertaken for tablet counts compared with the percentage of days on which openings were detected by the MEMS apparatus.

Results

Ninety-two patients were identified by general practitioners to receive tricyclic antidepressant therapy. Of these, two were excluded because of glaucoma and one because the most recent course of treatment had finished only 3 weeks earlier. Of the 89 patients entered into the study, one patient in the amitriptyline group was withdrawn by his spouse who would not allow the nurse to finish the first interview. The results reported are therefore for 88 patients of whom 59 were prescribed dothiepin and 29 amitriptyline. There were 61 women and 27 men with an average age of $46.1 \pm$ s.d.16.3 years (Table 1).

Of the 59 patients prescribed dothiepin, 40 (67.8%) completed 6 weeks therapy and 30 (50.8%) the 12 weeks study. Twenty-four of the 29 (82.8%) prescribed amitriptyline completed 6 weeks and 17 (58.6%) 12 weeks.

Reasons for stopping therapy

At each interview, patients were asked whether they were still taking their medication. Fourteen patients volunteered reasons for premature cessation of their antidepressant including side-effects (5), feeling better (3), lack of benefit (2), concerns about potential adverse effects (2), hospitalization (1) and going on holiday (1). In addition, three patients did not commence therapy: 1 because of previous side-effects, a second for fear of side-effects and the third did not want drug therapy.

Measurements of compliance

(a) *Self reporting* Morisky scores were available for 54 of the 59 patients prescribed dothiepin. One patient withdrew from the study, a second moved to north-east England, and two patients declined to be interviewed at 6 weeks: a fifth patient failed to commence therapy because of fear of side-effects. All 29 patients prescribed amitriptyline completed Morisky scores, the results for which are given in Table 2.

(b) *Tablet counts* Fifty-five patients prescribed dothiepin and all 29 patients supplied amitriptyline allowed their tablets to be counted. Two patients in the dothiepin group claimed to have thrown their medicine away and a third moved to another part of England. The results are shown in Table 2.

(c) *MEMS containers* Of those prescribed dothiepin, one patient threw the container away, and a second was returned in a damaged condition; two were defective. Good data for the number of openings were available for all the remaining patients prescribed dothiepin, and all 29 on amitriptyline. Two parameters were calculated. The first was the number of openings divided by the number of days on which therapy was taken; the second, the percentage of monitored days on which the container was opened. In general these measurements were fairly consistent one with the other.

Of the 59 patients prescribed dothiepin, 15 (25.4%) opened their containers on 100% of the days they claimed to be taking the treatment and 31 (52.5%) in over 90% of reported days. For the 29 amitriptyline patients, the figures were 9 (31.0%) and 13 (44.8%), respectively. Additional advantages of the MEMS system included the precise

Table 1 Patient characteristics.

	Dothiepin	*Amitriptyline*	*Total*
Number	59	29	88
Male:Female	19 : 40	8 : 21	27 : 61
Age $\pm$ s.d. (years)	46.5 ± 16.4	45.3 ± 16.5	46.1 ± 16.3
Number fulfilling DSM III criteria in the past month	29/59	12/29	41/88
Average dose at 6 weeks (mg)	93.1 ± 37.6 ($n=40$)	62.8 ± 26.6 ($n=24$)	
Number taking 100 mg or more daily	15	4	19

Table 2 Estimates of compliance at 6 weeks.

	Dothiepin	*Amitriptyline*	*Total*
(a) Total studied	59	29	88
Stopped by 6 weeks	19	5	24
Completed 6 weeks	40	24	64
Morisky scores			
0	31	16	47
1	18	9	27
2	4	2	6
>2	1	2	3
not available	5	0	5
(b) Tablet counts			
<50%	5	3	8
50–79%	5	4	9
80–99%	12	7	19
100	15	4	19
101–119	14	10	24
≥120	4	1	5
not possible	4	0	4
(c) MEMS days opened			
<50%	10	2	12
50–79%	5	11	16
80–99	24	7	31
100	16	9	25
defective	2	0	2
damaged	1	0	1
thrown away	1	0	1
(d) Blood samples			
taken	34	19	53
refused	10	6	16
not taken	12	3	15
not possib1e	4	1	5

timing of container opening, which in some patients was highly consistent (Figure 1) whilst in others was erratic, or showed patient-initiated drug holidays (Figure 2) and/or extra openings prior to review by the nurse interviewer. The early cessation of therapy was confirmed in several patients.

Comparisons were made between the MEMS data for the percentage of days the container was opened with

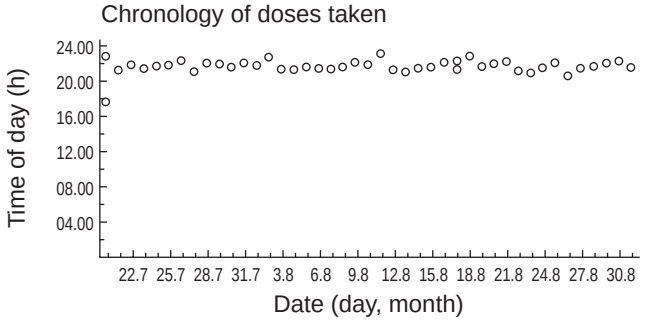

Figure 1 Chronology of doses taken. This patient shows a regular opening of the MEMS container at almost the same time of each evening.

Morisky scores (Table 3). Of the 47 patients whose Morisky scores were 0 (31 dothiepin and 16 amitriptyline), 21 (45.7%) showed 100% compliance and 33 (71.7%) over 90% compliance. By contrast, for the 35 patients with Morisky scores of 1 or greater, only 4 out of 35 (11.4%) showed 100% compliance and 11 (31.4%) >90% compliance. The sensitivity and specificity analyses are shown in Table 3.

There was a significant correlation between the tablet counts and percentage of days on which openings were detected by the MEMS apparatus ($r=0.616$; $P<0.001$). However, in 19 patients the number of tablets removed was very much higher than that indicated by opening of the MEMS containers.

(d) *Blood concentrations* Of the four measures employed to assess compliance, patients were least willing to cooperate with blood sampling, 16 (18.2%) refusing to have this undertaken at the 6 week review and 15 (17.0%) if they had already stopped taking their tablets. In addition, there were technical difficulties in obtaining sufficient blood from five patients. Thus, only 53 patients (60.2%) had blood taken in this study (Table 2).

Blood concentrations showed marked interindividual variability for the same dose of antidepressant but amongst those taking dothiepin, five showed a ratio of nordothiepin:dothiepin of 1.1 or greater. Of these, three showed no other evidence of poor compliance but two were poorly compliant, taking long drug holidays. Two other patients prescribed dothiepin exhibited very low plasma concentrations of both dothiepin and its metabolite, consistent with poor compliance, but showed a ratio of nordothiepin:dothiepin of <1.1.

Discussion

For tricyclic antidepressants to be effective it is generally considered that they must be taken for at least 90 days [2] and there is some evidence that outcome is affected by compliance [7, 11].

Various methods have been described for the assessment of compliance with drug therapy and in this study we have compared four of them. Of these, the MEMS system allowed us to identify the precise times at which opening of the container occurred. As a consequence it was possible to detect when patients ceased to take their medication, the occurrence of drug holidays, apparent increases in tablet consumption prior to review by our research nurses and a variability in the timing of drug taking during the study. As such it provided more detail of medicine taking behaviour than any other parameter studied. Thus this method approaches that of a 'gold standard' against which other methods can be compared. However, problems arose in three patients, two of whom threw their devices away and a third attempted to break into the circuitry. In

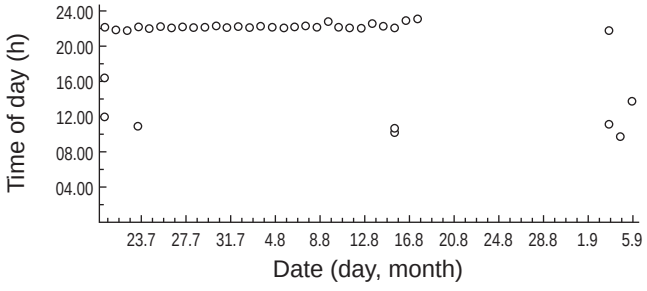

Figure 2 Chronology of doses taken. This patient shows a fairly regular pattern of openings for 3½ weeks. This was followed by a long 'drug holiday' and frequent openings in the period prior to the visit by the research nurse.

addition, two of the lids were defective, making further analysis impossible. Finally, the method is comparatively expensive which limits its routine usefulness.

Of the three other methods studied, the Morisky score was easy to derive and yielded a sensitivity of between 72% and 84% for detecting poor compliance, depending upon the arbitrary level of cut-off set for defining satisfactory compliance ($\geq$80%-100%, respectively). The specificity value of 74.1% at $\geq$ 80% compliance (the extent needed for long-term benefit [11]) suggests that for tricyclic antidepressants self-reporting is a useful screening technique and confirms the potential usefulness of this approach [12].

As in previous studies, tablet counts were difficult to interpret [13]. Although there was a reasonable correlation between the number of tablets removed from the containers and openings detected by the MEMS system, comparisons with the three other methods indicated that 19 patients discarded many of their tablets, thereby casting further doubt on the validity of this method for assessing compliance [13].

Of the four methods studied, the least satisfactory for the assessment of compliance in the setting of general practice was that of blood concentration measurement. Eighteen per cent of the patients were unwilling to allow blood sampling to occur and the nurses experienced some difficulties in sampling in the patients' homes. In those patients (60.2%) who had blood sampled, comparison with data obtained by the MEMS system showed that in several patients little credence could be given to the times at which they claimed to be taking their daily dose(s). Nevertheless, a low (or absent) parent drug concentration in relation to dose provided an indication of poor compliance. Furthermore, in the presence of low concentrations of parent drug, a ratio of nordothiepin to dothiepin of 1.1 or greater provided additional evidence. By contrast, when parent drug concentrations were high a ratio of nordothiepin to dothiepin of 1.1 or greater was of no help in assessing compliance.

Table 3 Moriskyscores [8] vs MEMS assessment of compliance.

	100% compliant	*'Non-compliant'*
(a) Morisky $\geq$ 1	4	31
Morisky 0	21	25
	Sensitivity 84.0%	Specificity 55.4%
	$\geq$ 90% compliant	*'Non-compliant'*
(b) Morisky $\geq$ 1	11	24
Morisky 0	33	13
	Sensitivity 75.0%	Specificity 64.9%
	$\geq$ 80% compliant	*'Non-compliant'*
(c) Morisky $\geq$ 1	15	20
Morisky 0	39	7
	Sensitivity 72.2%	Specificity 74.1%

The overall compliance rates at 6 weeks were higher than those previously reported for tricyclic antidepressants prescribed in British general practice [14]. This may reflect the beneficial effects of counselling given to 45 of these 88 patients [7]. Alternatively, there is a possibility of a Hawthorne effect. However, despite reasonable levels of patient compliance it is doubtful whether many would derive benefit as the doses of tricyclic antidepressants used (particularly amitriptyline) were low. Thus, although 14 patients were prescribed dothiepin in doses of 100 mg daily or greater, only 4 received amitriptyline in a dose of 100 mg daily. MacDonald and colleagues [15] using a record linkage scheme for prescribing in the Tayside area showed that only 7% of patients prescribed amitriptyline received it in adequate doses and our study provides further evidence of general practitioners' tendency to use low, often subtherapeutic, doses. Thus, even if compliance with antidepressant therapy is improved by the provision of printed information and/or counselling, the need for altered prescribing habits will remain.

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